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EXAMINER	
RAMACHANDRAN, UMAMAHESWARI	
ART UNIT	PAPER NUMBER
1617	
MAIL DATE	DELIVERY MODE
04/07/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/565,713	SCHELLER ET AL.	
	Examiner	Art Unit	
	UMAMAHESWARI RAMACHANDRAN	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-77* is/are pending in the application.

4a) Of the above claim(s) *16,36 and 68-77* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-35 and 37-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

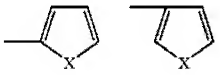
1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/28/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Restriction/Election

Applicants' election of group II, 17-28, 30-35, 37-57, 66 and 67claims in the reply filed on 1/7/2009 is acknowledged. Applicants' do not traverse the restriction between Group I (therapeutic combination) and other groups. Applicants' have traversed the restriction between Groups II-IV (methods of treating depression). Applicants' arguments regarding the restriction between Groups II-VI (methods of treating depression) have been found to be persuasive and the restriction election is withdrawn between Groups II-VI. The restriction between the therapeutic combination and method claims are maintained. Accordingly, Group I, claims 16, 36, 68-77 are withdrawn from consideration. Applicants' have provisionally elected with traverse, the species rotigotine as the amino tetralin compound, sertraline (antidepressant), endogenous depression (species for depression), depressive phases for bipolar disorder (affective disorder) for examination purposes. Applicants' argue that administration of 2-aminotetralin compound for the treatment of depression does not recite an additional active ingredient. In response, Claim 66 is towards a method of treating depression administering a compound of clam 17, further comprising administering one additional active ingredient comprising one or more antidepressants, antipsychotics, sedatives, anxiolytics and/or anti-migraine agents. Claims 35, 56, 57, claim administering one or more antidepressant, claims 58, 59 claim one or more antipsychotics, claims 60, 61 claim one or more sedatives, claims 62 and 63 claim one or more anxiolytics, claims 64 and 65 claim one or more anti-migraine agents.

Applicants' argue that the genus embraced by the formula is not so large and will not impose an undue burden search on the office. In response, the compounds of formula where R1 is a group



where X is S, O, NH.

When X is S the substituent is thienyl, X is O is furanyl and when X is NH it is pyrrolyl substitution. Hence the compounds are structurally different and possess different physical, chemical, functional properties, bioavailabilities, pharmacokinetic profiles, and pharmacological efficacy. Because the species have different structures and properties, different searches are required for each species, which presents a substantial burden to the Office. In addition, as stated above, in the combination therapy claimed, the office has to search the amino tetralin compounds in combination of a sedative, anti-psychotic, anti-migraine, anxiolytics and other additional antidepressants. The compounds are functionally different and each class encompasses a huge number of compounds and it will be a substantial search burden to the Office. The examiner contacted the Applicants' representative for election of species for anxiolytics, sedatives, antipsychotics and anti-migraine agents. Applicants' representative (Ann Roberts on behalf of Atty Jim Forbes on 3/18/2009) has elected clozapine (antipsychotics), dipenhydramine (sedative), fluspirilene (anxiolytic) and almotriptan (anti-migraine) agents. The restriction between methods of treating different types of depression is withdrawn and accordingly the election of species for depression and

affective disorder is withdrawn The restriction between the therapeutic combination and method claims and species for antidepressants (sertraline), antipsychotics (clozapine), sedative (dipenhydramine), anxiolytics (fluspirilene) and anti-migraine (almotriptan) agents are maintained.. The restriction is made Final. Claims 16-77 are pending, claims 16, 36, 68-77 and claims 17-35, 37-67 will be examined on the merits herein.

Application Priority

This application is a U.S. national stage filing under 35 U.S.C. §371 of International Application No. PCT/EP2004/008169 filed on July 22, 2004, which claims priority of German Application No. DE 103 34 187.0 filed on July 26, 2003.

Information Disclosure Statement

The information disclosure statement (IDS) filed on 1/28/2008 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the IDS is being considered by the Examiner.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to

be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 17-35, 37-67 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 10-82 of copending Application No. 10/565,699. Although the conflicting claims are not identical, they are not patentably distinct from each other because both teach a method of treating depression comprising administering rotigotine. Claims 17-25, 37-67 of the instant application teach a method of treating depression comprising administering compounds including rotigotine (elected species) and additional drugs that include antidepressants, antipsychotics, anxiolytics, anti-migraine and sedatives. Claims 10-82 of the co-pending application '699 teach a method of treating depression comprising administering rotigotine and additional drugs that include antidepressants, antipsychotics, anxiolytics, anti-migraine and sedatives.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure

would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and, (8) the quantity of experimentation necessary.

Claims 17-35, 37-67 are rejected under 35 U.S.C. 112, first paragraph, because specification while demonstrating the suitability of rotigotine as an antidepressant in three animal models (para 0015-18) does not reasonably provide enablement for treating depression with any other compounds listed in formula of claim 17. Also, the specification does not reasonably provide enablement for treating depression in a combination therapy as claimed (claims 35, 58-66) with addition of one or more antidpepressants, anxiolytics, sedatives, antipsychotics and anti-migraine agents. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

(1, 5) The nature of the invention and the breadth of the claims:

The instant claims are directed to a method of treating depression in a mammal comprising administering a compound of formula of claim 14. The dependent claims (35, 58-66) claim administration of additional ingredients such as antidepressants, anxiolytics, sedatives, antipsychotics and anti-migraine agents. The dependent claims then are directed to treatment of various kinds of depression that include somatogenic, psychogenic, endogenous, symptomatic, pharmacogenic etc. The claim 17 is broad with

respect to the compounds of formula of claim 14. Claims 35, 56-65 are very broad with respect to the addition of another ingredient in the treatment namely antidepressants (from various classes), sedatives, anti-psychotics. anti-migraine and anxiolytics compounds.

(3) The relative skill of those in the art:

The relative skill of those in the pharmaceutical and medical arts is high, requiring advanced education and training.

(4) The predictability of the art:

Despite the advance training of those in the art, the art is highly unpredictable. It is still not possible to predict the pharmacological activity or treatment efficacy of a compound based on the structure alone. It is also not possible to predict the efficacy of a given class of compounds for the treatment of a particular disease absent a mechanistic link between the pharmacological activity of the class of agents and the etiology or pathophysiology of the disease. Typically, in order to verify that a compound will be effective in treating a disease, the compounds must be either tested directly in a patient or in a model that has been established as being predictive of treatment efficacy. In order to predict whether a class of compounds would be effective in treating a disease, the etiology or pathophysiology of the disease must be uncovered, and there should be a nexus between the pharmacological activity of the class of agents and the etiology or pathophysiology of the disease. It is impossible to predict whether the compound or class of compounds based on the chemical structure that they would actually be effective for treating depression. It is not possible to predict that every single

substituted 2-amino tetralin compounds claimed can be combined with other antidepressants, (from various classes), sedatives, anti-psychotics. anti-migraine and anxiolytics compounds in treating depression. Joffe et al. (Acta Psychiatr Scand, 1997, Jun 95(6), 551-2) teaches adverse event reports of fluoxetine and evidence of a drug interaction between fluoxetine (an antidepressant) and sumatriptan (anti-migraine drug) suggesting that this combination is not entirely free of side-effects and should be used with caution when indicated (see Abstract). The document on antidepressants (http://en.wikipedia.org/wiki/Antidepressant) teaches that combination therapy is useful in treating patients for depression and further state that aalthough this may be used in clinical practice, there is little evidence for the relative efficacy or adverse effects of this strategy, The document lists various classes of antidepressants available for the treatment. The reference also teaches all the side effects associated with different classes of the antidepressant family. Accordingly, it would not be possible to one having ordinary skill in the art at the time of the invention what combination of substituted 2-amino tetraline compounds would have been effective in treating depression with the huge class of antidepressants available with more efficacy, less side effects and most importantly with less drug interactions. Preskorn (Antidepressants: Past, Present and Future) teaches that use of antidepressant combinations has become increasingly commonplace in young patients but this strategy is not recommended in the elderly due to the increased potential for orthostatic hypotension and side effects. Hence it is highly unpredictable what the outcome would be for older patients in antidepressant combination therapy. There is a high degree of unpredictability involved in a method of

treating a mammal for depression comprising administering a substituted 2-amino tetraline compounds with one or more antidepressants, sedatives, anti-psychotics. anti-migraine and anxiolytics

(2) The state of the prior art:

The prior art teaches the use of antidepressants in combination therapy. Van der Weide (E J of Pharmacology, 1988, 146, 319-326) teaches N-0437 (rotigotine) enantiomers are very promising candidates for psychotherapeutic use (see Abstract). Timmerman (chapter 9, E J of pharmacology, 181, 1989, 253-60) teaches N-0437 (rotigotine) as an antipsychotic drug. Hrdlicka (Eur Psychiatry, 2002, 17, 484) teaches combination therapy of clozapine (antipsychotic drug) in psychotic depression. The prior art Ranjan et al. (Biol Psychiatry, 1996, 40, 253-58) teaches clozapine in treating psychotic depression. Joffe et al. (Acta Psychiatr Scand, 1997, Jun 95(6), 551-2) teaches adverse event reports of fluoxetine and evidence of a drug interaction between fluoxetine (an antidepressant) and sumatriptan (anti-migraine drug) suggesting that this combination is not entirely free of side-effects and should be used with caution when indicated (see Abstract). There are prior art teachings of rotigotine with other compounds such as COX-2 inhibitors (US 20040034083), CB-1 antagonist (US 20040209861) in the treatment of Parkinson's disease, pramipexole or talipexole (dopamine 3 agonists) for the reduction of excessive food intake (US 20050032843) However, the prior art or the specification does not teach combination of the substituted 2-amino tetralin compounds with one or more antidepressants, sedatives, anti-psychotics. anti-migraine and anxiolytics

(6, 7) The amount of guidance presented and the presence of working examples:

It has been established that, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." *In re Fisher*, 427 F.2d 833, 839 166 USPQ 18, 24 (CCPA 1970). The specification states that substituted 2-amino tetralin compounds in particular rotigotine, are basically suitable for the treatment of the various forms of depression or for the treatment of affective disorders, in particular depressive episodes, recurrent depressive disorders, cyclothymia and depressive phases in bipolar affective disorders. The specification demonstrates the suitability of rotigotine as an antidepressant in three animal models (para 0015-18). However, the specification does not provide any combination therapy with rotigotine or any of the compounds claimed with any of the additional ingredients claimed in the treatment. The specification does not provide any guidance of how much dosage is effective of each additional antidepressant or sedative or anxiolytic or anti-migraine or anti-psychotic in combination therapy in any of the compounds claimed. The specification does not provide guidance to any adverse or drug interactions that may occur in combining the claimed compounds with other drugs. The specification does not provide any guidance to the dosage regimen to patient specific population as prior art teaches that combination therapy in elderly is not recommended due to the increased potential for orthostatic hypotension and side effects. In summary, Applicant has provided little guidance beyond what was recognized in the art at the time of filing.

(8) The quantity of experimentation needed:

In order to enable the instantly claimed methods commensurate with the entire scope, a large quantity of experimentation would be necessary. With Applicants' guidance provided in the specification and what is known in the prior art the person of ordinary skill in the art would have to conduct these experiments administering the substituted 2-amino tetralin compounds in mammals to verity the compounds are useful in treating depression. Applicants' have tested only one compound rotigotine (from the genus of the compounds claimed) in animal models for treating depression. Applicants' have not shown a combination therapy of rotigotine with one or more antidepressants, sedatives, anti-psychotics. anti-migraine and anxiolytics in treating depression. Considering the unpredictability of the combination of compounds due to the drug interactions, this would be an arduous and daunting task. It would require undue experimentation to test substituted 2-amino tetralin compounds including rotigotine to obtain effective dosage for all set of patient population (including elderly) for treating depression in combination with other drugs. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention of treating a subject for depression administering substituted 2-amino tetralin compounds in monotherapy and in combination therapy as claimed. Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

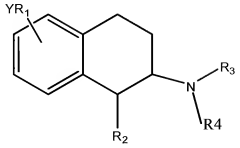
The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

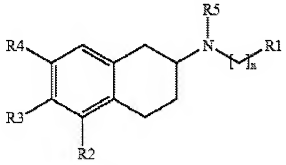
Claims 17-34, 37-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weide et al. (E J of Pharmacology, 146, 1988, 319-326) and Andersson et al. (Applicant cited IDS: EP 03334538) and Sherman et al. (Clinical Psychiatry News, Nov 1 2001) in view of Lauterbach et al. (Applicant cited IDS: WO 02/089777).

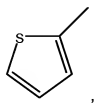
Weide et al. teaches enantiomers of N-0437 (rotigotine), d2 dopamine receptor agonist stimulates presynaptic dopamine receptors and blocks postsynaptic receptors and these properties make the enantiomers of N-0437 very promising candidates for psychotherapeutic use (see abstract).

Andersson et al. teaches compounds with the formula



Where YR1 is OR1, R2 is H or C1-C3 alkyl, R3 is -CH2- (C3-C8 cycloalkyl); and R4 is hydrogen, C1-Cs alkyl, -CH2- (C3-C4 cycloalkyl), - (CH2)m R5 or-CH2-CH2-X-(CH2) nCH3; where-in n is zero to 3; m is 2 or 3; X is oxygen or sulfur, and R6 is 2-thiophenyl, 3-thiophenyl, phenyl or phenyl substituted by one or two substituents selected from chlorine, bromine, fluorine, C1-C3 alkoxy and C1-C3 alkyl; Furthermore, Andersson teaches that the compounds are useful as a medicament for use as an anxiolytic or anti-depressant. Accordingly, the Andersson et al. reference for example, teaches a compound of formula, Applicants' claim a compound of formula



Where R3=R4 = H, R2 = OH, R5 = 

, R1 is C1-C3 alkyl.

Andersson does not teach the claimed compounds but the compounds of Andersson are structurally similar to compounds of claim 14.

Sherman in Clinical Psychiatry news reports that pramipexole, a dopamine agonist (affects D2 and D3 receptors) and has been approved for Parkinson's disease has been found to be comparable to fluoxetine in the treatment of depression. The article also states that pramipexole, may be an effective augmentation agent for patients with treatment-resistant depression in combination therapy.

It would have been obvious to one having ordinary skill in the art at the time of the invention that compound such as rotigotine can be used in treating depression from the prior art teachings. Weide et al. teaches rotigotine (N-0437), d2 dopamine receptor agonist as a very promising candidate for psychotherapeutic use. Andersson et al. teaches structurally similar compounds are useful in treating depression. Sherman teaches a D2/D3 agonist that has been approved for Parkinson's disease has comparable effects to that of fluoxetine in treating depression. Accordingly, one having ordinary skill in the art would have been motivated to use rotigotine in treating depression in a mammal as the compound is a D2 agonist, has been shown in the prior art to be useful in treating Parkinson's disease and furthermore it is structurally similar to Andersson compounds . It would have been obvious to one having ordinary skill in the art at the time of the invention to have used rotigotine in treating various subtypes of depression namely endogenous, somatogenic, symptomatic, or psychogenic depression. It is known in the art (McAllister-Williams, http://www.netdoctor.co.uk/diseases/depression/classification_000001.htm) and also from Applicant's specification

(para 0028) that endogenous, somatogenic, symptomatic, or psychogenic depression are all subtypes of depression. The document by McAllister Williams teach that bipolar affective disorder is another subtype of depression and patients with depression have anxiety symptoms. Hence it would have been obvious to one having ordinary skill in the art to administer rotigotine for treating different subtypes of depression or affective disorder such as bipolar affective disorder. It would have been obvious to one having ordinary skill in the art that a drug capable of treating depression would treat the condition irrespective of what the condition is associated with. For example, fluoxetine (SSRI), an antidepressant drug is useful in treating major depression. Fisch (J Clin Oncol. 2003 May 15;21(10):1937-43) teaches fluoxetine in treating depression (symptomatic depression) in cancer patients and Sobow (Int J of Geriatr Psychiatry, 2001, 1108-1109) teaches the effectiveness of fluoxetine in patients with Alzheimer's disease. It would have been obvious to one having ordinary skill in the art that a drug such as fluoxetine capable of treating depression associated with cancer patients would be effective in treating depression associated with Alzheimer patients. One having ordinary skill in the art would have been motivated to use rotigotine in treating depression in general including the subtypes in achieving similar therapeutic benefits. Weide et al. teaches both enantiomers of rotigotine are very promising candidates for psychotherapeutic use. Hence it would have been obvious to one having ordinary skill in the art to use at least 90% of S enantiomer.

Weide, Andersson et al. and Sherman et al. do not teach the rotigotine dosage regimen, formulation type and administration.

Lauterbach et al. teaches silicone based transdermal therapeutic system comprising two or more silicone adhesives comprising rotigotine and administration of the drug to a patient. The reference teach daily dosages of 4.5, 9.0 and 13.5 and 18 mg patches can be administered (p 15, lines 5-10).

It would have been obvious to one having ordinary skill in the art at the time of the invention to have formulated as an ointment or a plaster having the active ingredient rotigotine for transdermal administration in treating depression because Lauterbach et al. teaches transdermal therapeutic system comprising rotigotine and further teach the dosage amounts for administration to a patient. Accordingly, one having ordinary skill in the art would have been motivated to administer the drug transdermally in the claimed amounts because it has been shown in the prior art that such formulation is possible and the drug dosage claimed is a safe amount.

Claims 35, 56, 57, 66, 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weide et al. (E J of Pharmacology, 146, 1988, 319-326) and Andersson et al. (Applicant cited IDS: EP 03334538) and Sherman et al. (Clinical Psychiatry News, Nov 1 2001) 1 2001) in view of Lauterbach et al. (Applicant cited IDS: WO 02/089777) as applied to claims 17-34, 37-54 above and in view of Maj (US 6,255,329).

Weide et al, Andersson et al, Sherman et al. and Lauterbach et al. teachings discussed as above.

The references do not teach addition of one or more antidepressants to compounds of formula of claim 17 in treating depression.

Maj teaches treatment of depression in patients comprising administering pramipexole and sertraline (see abstract, col. 4, claim 10). Maj teaches that in combination therapy, the agents can be co-administered separately or as components of a single pharmaceutical dosage form and the drugs can be in different dosage forms (col.2. lines 11-30).

It would have been obvious to one having ordinary skill in the art to treat depression comprising administering compounds of formula of claim 14, such as rotigotine along with one or more antidepressant , sertraline (elected species) in treating depression because of the teachings of Maj. Maj teaches treating depression comprising administering pramipexole (useful for treating Parkinson's disease) and sertraline. Rotigotine, the elected species is known in the art to treat Parkinson's disease (Lauterbach). One having ordinary skill in the art would have been motivated to use rotigotine for another drug (pramipexole) used in Parkinson's disease in combination with sertraline in treating depression because of expectation of therapeutic benefits, synergistic or additive effects. It would have been obvious to one having ordinary skill in the art at the time of the invention to have administered one of the additional active ingredients in separate dosage forms by the same or different routes at the same or different times because of Maj's teachings. Maj teaches that in treating depression with sertraline the agents can be co-administered separately or as components of a single pharmaceutical dosage form and the drugs can be in different dosage forms. Also, It is well within the skilled medical professional to determine suitable dosing regimens. It would have been customary for an artisan of ordinary skill

to determine the optimal dosage of the drug in order to best achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, this optimization of route of delivery, dosage regimens would have been obvious at the time of applicant's invention.

Claims 58, 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weide et al. (E J of Pharmacology, 146, 1988, 319-326) and Andersson et al. (Applicant cited IDS: EP 03334538) and Sherman et al. (Clinical Psychiatry News, Nov 1 2001) 1 2001) in view of Lauterbach et al. (Applicant cited IDS: WO 02/089777) as applied to claims 17-34, 37-54 above and in view of Hrdlicka (Eur Psychiatry, 2002, 17).

Weide et al, Andersson et al, Sherman et al. and Lauterbach et al. teachings discussed as above.

The references do not teach addition of one or more anti-psychotics in treating depression.

Hrdlicka teaches combination of clozapine and maprotiline (a tricyclic antidepressant) in refractory psychotic depression treatment. The reference teaches that clozapine is antipsychotic agent and when administered along with maprotoline to a patient with recurrent depressive disorder.

It would have been obvious to one having ordinary skill in the art to treat depression comprising administering compounds of formula of claim 14, such as rotigotine along with an antipsychotic agent, clozapine (elected species) in treating depression because of the teachings of Hrdlicka. Hrdlicka teaches treating depressive disorder comprising administering clozapine and maprotiline (a tricyclic antidepressant).

One having ordinary skill in the art would have been motivated to use rotigotine in combination with an anti-psychotic drug such as clozapine because clozapine has been shown to be useful in combination anti-depressant therapy and in expectation of similar therapeutic benefits in combination with rotigotine in treating depression. Also, Timmerman (chapter 9, E J of pharmacology, 181, 1989, 253-60) teaches N-0437 (rotigotine) as an antipsychotic drug. One having ordinary skill in the art would have been motivated to administer one anti-psychotic drug (rotigotine) for clozapine in Hrdlicka's method of treating psychotic depression treatment in expectation of similar and or better therapeutic benefits of treating depression.

Claims 60 and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weide et al. (E J of Pharmacology, 146, 1988, 319-326) and Andersson et al. (Applicant cited IDS: EP 03334538) and Sherman et al. (Clinical Psychiatry News, Nov 1 2001) 1 2001) in view of Lauterbach et al. (Applicant cited IDS: WO 02/089777) as applied to claims 17-34, 37-54 above and in view of Kupfer (Ann Clin Psychiatry, 1999, 11(4), 267-76).

Weide et al, Andersson et al, Sherman et al. and Lauterbach et al. teachings discussed as above.

The references do not teach addition of one or more sedatives in treating depression.

Kupfer teaches that depressed patients often report problems sleeping and epidemiologic evidence suggests that insomnia may precede the onset of depression (see Abstract).

It would have been obvious to one having ordinary skill in the art to treat depression comprising administering compounds of formula of claim 14, such as rotigotine along with a sedative agent, such as diphenhydramine (elected species) in combination therapy of treating depression because of the teachings of Kupfer. Kupfer teaches that depressed patients often report problems sleeping and it is known in the art that diphenhydramine is a sedative (US 20020177626). One having ordinary skill in the art would have been motivated to use a sedative agent along with an antidepressant in combination therapy in treating depressive patients is to help the patients and improve the quality of sleep in the patients.

Claims 62 and 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weide et al. (E J of Pharmacology, 146, 1988, 319-326) and Andersson et al. (Applicant cited IDS: EP 03334538) and Sherman et al. (Clinical Psychiatry News, Nov 1 2001) 1 2001) in view of Lauterbach et al. (Applicant cited IDS: WO 02/089777) as applied to claims 17-34, 37-54 above and in view of Zimmerman et al. (Am J Psychiatry 160:504-512, March 2003).

Weide et al, Andersson et al, Sherman et al. and Lauterbach et al. teachings discussed as above.

The references do not teach addition of one or more anxiolytics in treating depression.

Zimmerman teaches that compared to the depressed patients without generalized anxiety disorder, the depressed patients with modified generalized anxiety disorder had higher levels of suicidal ideation; poorer social functioning; a greater

frequency of other anxiety disorders, eating disorders, and somatoform disorders (See abstract).

It would have been obvious to one having ordinary skill in the art to treat depression comprising administering compounds of formula of claim 14, such as rotigotine along with an anxiolytic agent, such as fluspirilene in combination therapy of treating depression because the prior art teachings teach that the depressed patients with modified generalized anxiety disorder had higher levels of suicidal ideation; poorer social functioning; a greater frequency of other anxiety disorders, eating disorders, and somatoform disorders. Fluspirilene is known in the art as an anxiolytic agent (Lehmann, *Neuropsychobiology* 1989;21:197-204, Abstract). One having ordinary skill in the art would have been motivated to use an anxiolytic agent along with an antidepressant in combination therapy in treating depressive patients to provide therapeutic benefits for anxiety disorder.

Claims 64 and 65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weide et al. (E J of Pharmacology, 146, 1988, 319-326) and Andersson et al. (Applicant cited IDS: EP 03334538) and Sherman et al. (Clinical Psychiatry News, Nov 1 2001) 1 2001) in view of Lauterbach et al. (Applicant cited IDS: WO 02/089777) as applied to claims 17-34, 37-54 above and in view of document, Links between Depression and Migraine (5/19/2003).

Weide et al, Andersson et al, Sherman et al. and Lauterbach et al. teachings discussed as above.

The references do not teach addition of one or more anti-migraine in treating depression.

Links between Depression and Migraine document teaches that risk of migraine in individuals with pre-existing major depression was three times higher than in individuals with no history of depression and the risk of major depression in persons with pre-existing migraine was more than fivefold higher than in people with no history of headaches.

It would have been obvious to one having ordinary skill in the art to treat depression comprising administering compounds of formula of claim 14, such as rotigotine along with an anti-migraine agent, such as almoptriptan in combination therapy of treating depression because the prior art teachings teach the connection between migraine and depression. Almotriptan is known in the prior art as an anti-migraine agent (US 20030225002). The document Links between Depression and Migraine teaches that patients with depression had higher risk of migraine. One having ordinary skill in the art would have been motivated to use an anti-migraine agent along with an antidepressant in combination therapy in treating depressive patients to provide therapeutic benefits for migraine.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to UMAMAHESWARI RAMACHANDRAN whose

telephone number is (571)272-9926. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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